

PATENT  
Attorney Docket No. 401371/NIH

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

BURKE, Jr., et al.

Art Unit: Unassigned

Application No. Unassigned

Examiner: Unassigned

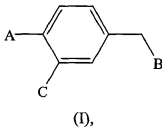
Filed: Herewith

For: PHENYLALANINE DERIVATIVES

AMENDMENTS TO CLAIMS MADE  
VIA PRELIMINARY AMENDMENT

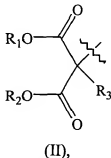
Amendments to existing claims:

1. (Amended) A compound of formula I:



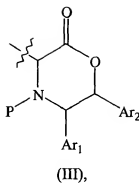
wherein:

A is carboxyl, carboxyalkyl, dicarboxyalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, dialkoxy carbonylalkyl, or a malonyl group of formula II:

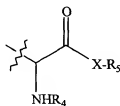


wherein R<sub>1</sub> and R<sub>2</sub> may be the same or different and are selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and R<sub>3</sub> is selected from the group consisting of hydrogen, halo, hydroxy, amino, alkyl, aryl, and alkoxy;

B has the formula III:



wherein P is an amine ~~protective-protecting~~ group; and Ar<sub>1</sub> and Ar<sub>2</sub> are aryl groups; or the formula IV:



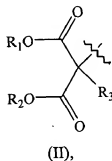
wherein X is NH or O; R<sub>4</sub> is hydrogen, alkyl, aryl, alkylaryl, arylalkyl, or an amine protective group; and R<sub>5</sub> is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and

C is selected from the group consisting of hydrogen, hydroxyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkoxy, alkoxy, and alkoxyalkyl;

wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of alkyl, hydroxy, halo, keto, amino, and alkoxy; with the provisos that (i) R<sub>5</sub> is not hydrogen when A is carboxyl or carboxyalkyl, C is hydrogen, B has the formula IV wherein R<sub>4</sub> is hydrogen or alkylcarbonyl, and X is NH; and (ii) R<sub>5</sub> is not hydrogen or alkyl when A is carboxyl or carboxyalkyl, C is hydrogen or hydroxy, B has the formula IV wherein R<sub>4</sub> is hydrogen or alkylcarbonyl, and X is O.

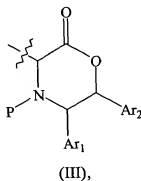
2. (Amended) The compound of claim 1, wherein:

A is carboxyl, carboxyl C<sub>1</sub>-C<sub>6</sub> alkyl, dicarboxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> dialkoxycarbonyl C<sub>1</sub>-C<sub>6</sub> alkyl, or a malonyl group of formula II:

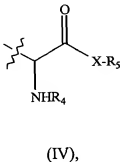


wherein R<sub>1</sub> and R<sub>2</sub> may be the same or different and are selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, and heteroaryl; and R<sub>3</sub> is selected from the group consisting of hydrogen, halo, hydroxy, amino, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, and C<sub>1</sub>-C<sub>6</sub> alkoxy;

B has the formula III:



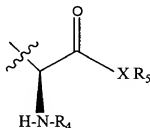
wherein P is an amine ~~protective-protecting~~ group; and Ar<sub>1</sub> and Ar<sub>2</sub> are aryl groups; or B has the formula IV:



wherein X is NH or O; R<sub>4</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, or an amine ~~protective-protecting~~ group; and R<sub>5</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, and heteroaryl; and

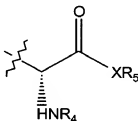
C is selected from the group consisting of hydrogen, hydroxyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyloxy, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl C<sub>1</sub>-C<sub>6</sub> alkyl; wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, halo, keto, amino, and C<sub>1</sub>-C<sub>6</sub> alkoxy.

4. (Amended) The compound of claim 3, wherein B has the formula:



wherein X is NH or O; R<sub>4</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, or an amine ~~protective-protecting~~ group; and R<sub>5</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, and heteroaryl.

5. (Amended) The compound of claim 3, wherein B has the formula:

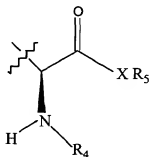


wherein X is NH or O; R<sub>4</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, or an amine ~~protective-protecting~~ group; and R<sub>5</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, and heteroaryl.

6. (Amended) The compound of claim ~~4 or 5~~, wherein X is O.

9. (Amended) The compound of claim 8, wherein ~~acid~~ the amine protecting group is selected from the group consisting of fluorenylmethoxycarbonyl, tert-butoxycarbonyl, carbobenzoxy, and carbamoyl.

24. (Amended) The compound of claim ~~1 or 2~~, wherein R<sub>1</sub> and R<sub>2</sub> are tert-butyl ~~and~~, R<sub>3</sub> is hydrogen, and B has the formula



wherein X is O, R<sub>4</sub> is fluorenylmethoxycarbonyl, and R<sub>5</sub> is hydrogen.

34. (Amended) A conjugate comprising a conjugant covalently linked to a compound of ~~any of claims 1-25~~ claim 1.

44. (Amended) The compound of ~~any of claims 41-43~~ claim 41, wherein E is hydrogen.

46. (Amended) The compound of ~~any of claim 41-45~~ claim 41, wherein R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are hydrogen.

48. (Amended) The compound of ~~any of claims 38-47~~ claim 38, wherein W is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, oxalyl, C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, arylaminooxalyl, aryl C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, C<sub>1</sub>-C<sub>6</sub> alkoxyoxalyl, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryloxy carbonyl, and aryl C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C<sub>1</sub>-

C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and keto; and the heterocyclcyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S.

66. (Amended) The compound of ~~any of claims 38-65~~ claim 38, wherein Z is aryl C<sub>1</sub>-C<sub>6</sub> alkylamino.

71. (Amended) The compound of ~~any of claims 38-65~~ claim 38, wherein Z is aryl heterocyclcyl C<sub>1</sub>-C<sub>6</sub> alkylamino.

77. (Amended) The compound of ~~any of claims 38-76~~ claim 38, wherein said amino acid is selected from the group consisting of glycine, alanine, valine, norvaline, leucine, iso-leucine, norleucine,  $\alpha$ -amino n-decanoic acid, serine, homoserine, threonine, methionine, cysteine, S-acetylaminomethyl-cysteine, proline, trans-3- and trans-4-hydroxyproline, phenylalanine, tyrosine, 4-aminophenylalanine, 4- nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine,  $\beta$ -phenylserine  $\beta$ -hydroxyphenylalanine, phenylglycine,  $\alpha$ -naphthylalanine, cyclohexylalanine, cyclohexylglycine, tryptophan, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid, asparagine, aminomalonic acid, aminomalonic acid monoamide, glutamic acid, glutamine, histidine, arginine, lysine, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine,  $\alpha$ -aminocyclopentane carboxylic acid,  $\alpha$ -aminocyclohexane carboxylic acid,  $\alpha$ -aminocycloheptane carboxylic acid,  $\alpha$ -(2-amino-2-norbornane)-carboxylic acid,  $\alpha$ , $\gamma$ -diaminobutyric acid ~~and~~,  $\alpha$ , $\beta$ -diaminopropionic acid, homophenylalanine, and  $\alpha$ -tert-butylglycine.

84. (Amended) A composition comprising a pharmacologically acceptable carrier and a compound of ~~any of claims 38-83~~ claim 38.

85. (Amended) A method for inhibiting an SH2 domain from binding with a phosphoprotein comprising contacting an SH2 domain with a compound of ~~any of claims 34-83~~ claim 38.

90. (Amended) A method for inhibiting SH2 domain binding comprising exposing a material containing an SH2 domain to a compound of ~~any of claims 34-83~~ claim 38.

91. (Amended) A method for determining the presence of an SH2 domain in a material comprising:

- (a) exposing a sample of said material to a SH2 binding compound and obtaining a first binding result;
- (b) exposing another sample of said material to a compound of ~~any of claims 34-83~~ claim 38 and obtaining a second binding result; and
- (c) comparing the first and second binding results to determine whether an SH2 domain is present in the material.

92. (Amended) A method of preventing or treating a disease, state, or condition in a mammal comprising administering a compound of ~~any of claims 34-83~~ claim 38.

106. (Amended) A method of enhancing the therapeutic effect of a treatment rendered to a mammal that has been afflicted with a disease, state, or condition, comprising administering to the mammal a compound of ~~any of claims 38-83~~ claim 38 in conjunction with the treatment.

112. (Amended) A method of inhibiting the MAP kinase activity in a mammal comprising administering to the mammal a compound of ~~any of claims 34-83~~ claim 38.

09937150.032602

**PATENT**  
 Attorney Docket No. 401371/NIH

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

BURKE, Jr., et al.

Art Unit: Unassigned

Application No. Unassigned

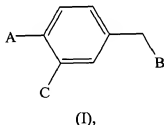
Examiner: Unassigned

Filed: Herewith

For: PHENYLALANINE DERIVATIVES

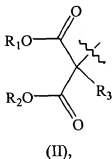
**PENDING CLAIMS AFTER ENTRY OF PRELIMINARY AMENDMENT**

1. A compound of formula I:



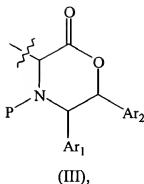
wherein:

A is carboxyl, carboxyalkyl, dicarboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, dialkoxycarbonylalkyl, or a malonyl group of formula II:

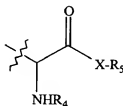


wherein R<sub>1</sub> and R<sub>2</sub> may be the same or different and are selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and R<sub>3</sub> is selected from the group consisting of hydrogen, halo, hydroxy, amino, alkyl, aryl, and alkoxy;

B has the formula III:



wherein P is an amine protecting group; and Ar<sub>1</sub> and Ar<sub>2</sub> are aryl groups; or the formula IV:



(IV),

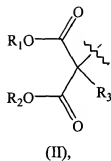
wherein X is NH or O; R<sub>4</sub> is hydrogen, alkyl, aryl, alkylaryl, arylalkyl, or an amine protective group; and R<sub>5</sub> is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and

C is selected from the group consisting of hydrogen, hydroxyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkoxycarbonyl, and alkoxycarbonyl alkyl;

wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of alkyl, hydroxy, halo, keto, amino, and alkoxy; with the provisos that (i) R<sub>5</sub> is not hydrogen when A is carboxyl or carboxyalkyl, C is hydrogen, B has the formula IV wherein R<sub>4</sub> is hydrogen or alkylcarbonyl, and X is NH; and (ii) R<sub>5</sub> is not hydrogen or alkyl when A is carboxyl or carboxyalkyl, C is hydrogen or hydroxy, B has the formula IV wherein R<sub>4</sub> is hydrogen or alkylcarbonyl, and X is O.

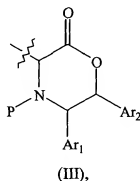
2. The compound of claim 1, wherein:

A is carboxyl, carboxyl C<sub>1</sub>-C<sub>6</sub> alkyl, dicarboxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> dialkoxycarbonyl C<sub>1</sub>-C<sub>6</sub> alkyl, or a malonyl group of formula II:

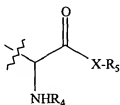


wherein  $R_1$  and  $R_2$  may be the same or different and are selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl, aryl, aryl  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylaryl, and heteroaryl; and  $R_3$  is selected from the group consisting of hydrogen, halo, hydroxy, amino,  $C_1$ - $C_6$  alkyl, aryl, and  $C_1$ - $C_6$  alkoxy;

B has the formula III:



wherein P is an amine protecting group; and  $Ar_1$  and  $Ar_2$  are aryl groups; or B has the formula IV:



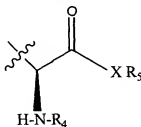
wherein X is NH or O;  $R_4$  is hydrogen,  $C_1$ - $C_6$  alkyl, aryl,  $C_1$ - $C_6$  alkylaryl, aryl  $C_1$ - $C_6$  alkyl, or an amine protecting group; and  $R_5$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl, aryl, aryl  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylaryl, and heteroaryl; and

C is selected from the group consisting of hydrogen, hydroxyl,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylcarbonyl,  $C_1$ - $C_6$  alkylcarbonyloxy,  $C_1$ - $C_6$  alkoxy carbonyl, and  $C_1$ - $C_6$  alkoxy carbonyl  $C_1$ -

C<sub>6</sub> alkyl; wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, halo, keto, amino, and C<sub>1</sub>-C<sub>6</sub> alkoxy.

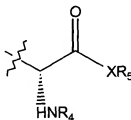
3. The compound of claim 2, wherein B has the formula IV.

4. The compound of claim 3, wherein B has the formula:



wherein X is NH or O; R<sub>4</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, or an amine protecting group; and R<sub>5</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, and heteroaryl.

5. The compound of claim 3, wherein B has the formula:



wherein X is NH or O; R<sub>4</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, or an amine protecting group; and R<sub>5</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, and heteroaryl.

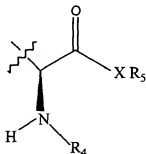
6. The compound of claim 4, wherein X is O.

7. The compound of claim 6, wherein R<sub>4</sub> is hydrogen.

8. The compound of claim 6, wherein  $R_4$  is an amine protecting group.

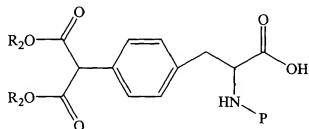
9. The compound of claim 8, wherein the amine protecting group is selected from the group consisting of fluorenylmethoxycarbonyl, tert-butoxycarbonyl, carbobenzoxy, and carbamoyl.

24. The compound of claim 1, wherein  $R_1$  and  $R_2$  are tert-butyl,  $R_3$  is hydrogen, and B has the formula



wherein X is O,  $R_4$  is fluorenylmethoxycarbonyl, and  $R_5$  is hydrogen.

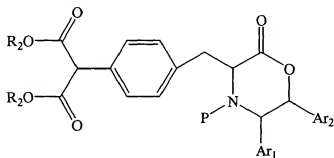
26. A process for preparing a compound of formula VIII:



(VIII),

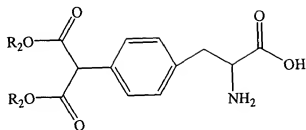
wherein  $R_2$  is alkyl and P is an amine protecting group; the process comprising:

(a) reducing the compound of formula



(VII),

to obtain a compound of formula IX:

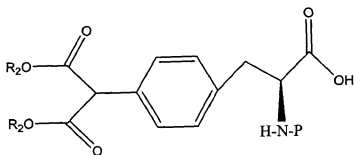


(IX);

and

(b) reacting the compound of formula IX with an amine protecting agent to obtain the compound of formula VIII.

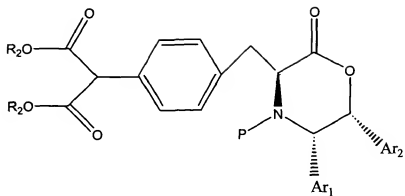
29. A process for preparing a compound of formula VIIIa:



(VIIIa)

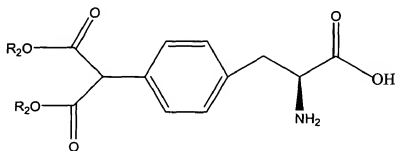
wherein  $R_2$  is alkyl and P is an amine protecting group; the process comprising:

(a) reducing a compound of formula VII



(VIIa)

to obtain a compound of formula IXa:

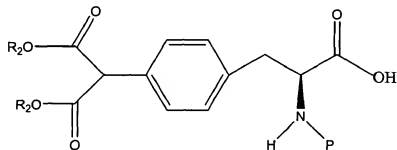


(IXa);

and

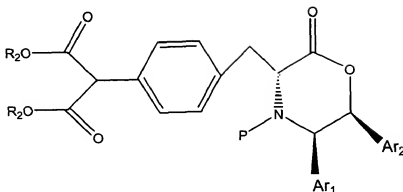
(b) reacting the compound of formula IXa with an amine protecting agent to obtain the compound of formula VIII.

30. A process for preparing a compound of the formula:

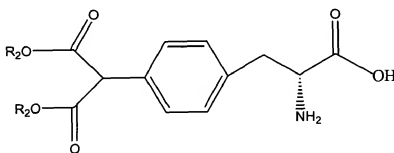


wherein  $R_2$  is alkyl and P is an amine protecting group; the process comprising:

(a) reducing a compound of formula:



to obtain a compound of formula IXb:

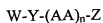


(IXb);

and (b) reacting the compound of formula IXa with an amine protecting agent to obtain the compound of formula VIII.

34. A conjugate comprising a conjugant covalently linked to a compound of claim 1.

38. A compound of the formula:



wherein n is 0 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, and a carboxyl end, the phenyl ring having one or more substituents selected from the group consisting of hydroxyl, carboxyl, formyl, carboxyalkyl, carboxyalkyloxy, dicarboxyalkyl, dicarboxyalkyloxy, dicarboxyhaloalkyl, dicarboxyhaloalkyloxy, and phosphonoalkyl, phosphonohaloalkyl, wherein the alkyl portion of the substituents may be unsubstituted or

substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, alkyl, alkoxy, and keto;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of alkylcarbonyl, oxalyl, alkylaminooxalyl, arylaminooxalyl, arylalkylaminooxalyl, alkoxyoxalyl, carboxyalkyl carbonyl, heterocyclyl carbonyl, heterocyclylalkyl carbonyl, arylalkyl heterocyclylalkyl carbonyl, aryloxy carbonyl, and arylalkoxy carbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, alkyl, alkoxy, and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

Z is an arylalkylamino or arylheterocyclyl alkylamino;

or a salt thereof;

with the proviso that W is not arylalkylamino when the phenyl ring of phenylalanyl contains a phosphonoalkyl or phosphonohaloalkyl substituent at a position para to the alkylamido group and the ortho and meta positions are unsubstituted.

39. The compound of claim 38, wherein n is 0 to 15;

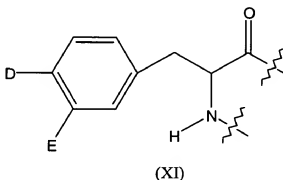
Y is a phenylalanyl radical having a phenyl ring, an amine end, and a carboxyl end, the phenyl ring having one or more substituents selected from the group consisting of hydroxyl, carboxyl, formyl, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl, carboxy C<sub>1</sub>-C<sub>6</sub> alkoxy, dicarboxy C<sub>1</sub>-C<sub>6</sub> alkyl, dicarboxy C<sub>1</sub>-C<sub>6</sub> alkoxy, dicarboxyhalo C<sub>1</sub>-C<sub>6</sub> alkyl, dicarboxyhalo C<sub>1</sub>-C<sub>6</sub> alkoxy, and phosphono C<sub>1</sub>-C<sub>6</sub> alkyl, phosphonohalo C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the alkyl portion of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and keto;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, oxalyl, C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, arylaminooxalyl, aryl C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, C<sub>1</sub>-C<sub>6</sub> alkoxyoxalyl, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryloxy carbonyl, and aryl C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy,

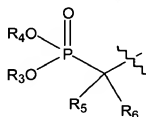
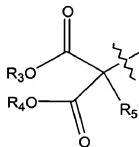
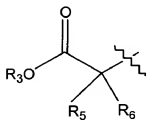
and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and  
Z is an aryl C<sub>1</sub>-C<sub>6</sub> alkylamino or arylheterocyclyl C<sub>1</sub>-C<sub>6</sub> alkylamino;  
or a salt thereof.

40. The compound of claim 39, wherein Y is of the formula XI:



wherein D has the formula XII, XIII, or XIV:



(XII)

(XIII)

(XIV)

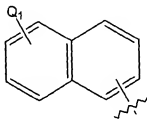
wherein R<sub>3</sub> and R<sub>4</sub> may be the same or different and are selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkaryl, and heteroaryl; and R<sub>5</sub> and R<sub>6</sub> may be the same or different and are selected from the group consisting of hydrogen, halo, hydroxy, amino, and C<sub>1</sub>-C<sub>6</sub> alkoxy; and

E is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, carboxyl, and C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl C<sub>1</sub>-C<sub>6</sub> alkyl.

41. The compound of claim 40, wherein D is of formula XII.

0037150-032602

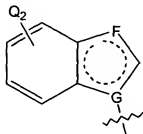
42. The compound of claim 40, wherein D is of formula XIII.
43. The compound of claim 40, wherein D is of formula XIV.
44. The compound of claim 41, wherein E is hydrogen.
45. The compound of claim 41, wherein E is carboxyl.
46. The compound of claim 41, wherein R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are hydrogen.
47. The compound of claim 43, wherein R<sub>3</sub> and R<sub>4</sub> are hydrogen.
48. The compound of claim 38, wherein W is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, oxalyl, C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, arylaminooxalyl, aryl C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, C<sub>1</sub>-C<sub>6</sub> alkoxyoxalyl, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryloxy carbonyl, and aryl C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S.
66. The compound of claim 38, wherein Z is aryl C<sub>1</sub>-C<sub>6</sub> alkylamino.
67. The compound of claim 66, wherein the aryl portion of Z has the formula:



wherein Q<sub>1</sub> is hydrogen or a substituent selected from the group consisting of hydroxyl, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, and C<sub>1</sub>-C<sub>6</sub> acylamino.

71. The compound of claim 38, wherein Z is aryl heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkylamino.

72. The compound of claim 71, wherein the heterocyclyl portion of Z has the formula:



wherein Q<sub>2</sub> is hydrogen or a substituent selected from the group consisting of hydroxyl, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, and C<sub>1</sub>-C<sub>6</sub> acylamino, and F and G are independently selected from the group consisting of C, N, O, and S.

77. The compound of claim 38, wherein said amino acid is selected from the group consisting of glycine, alanine, valine, norvaline, leucine, iso-leucine, norleucine,  $\alpha$ -amino n-decanoic acid, serine, homoserine, threonine, methionine, cysteine, S-acetylaminomethyl-cysteine, proline, trans-3- and trans-4-hydroxyproline, phenylalanine, tyrosine, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine,  $\beta$ -phenylserine  $\beta$ -hydroxyphenylalanine, phenylglycine,  $\alpha$ -naphthylalanine, cyclohexylalanine, cyclohexylglycine, tryptophan, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid, asparagine, aminomalonic acid, aminomalonic acid monoamide, glutamic acid, glutamine, histidine, arginine, lysine, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine,  $\alpha$ -aminocyclopentane carboxylic acid,  $\alpha$ -aminocyclohexane carboxylic acid,  $\alpha$ -aminocycloheptane carboxylic acid,  $\alpha$ -(2-amino-2-norbornane)-carboxylic acid,  $\alpha,\gamma$ -diaminobutyric acid,  $\alpha,\beta$ -diaminopropionic acid, homophenylalanine, and  $\alpha$ -tert-butylglycine.

84. A composition comprising a pharmacologically acceptable carrier and a compound of claim 38.

85. A method for inhibiting an SH2 domain from binding with a phosphoprotein comprising contacting an SH2 domain with a compound of claim 38.

90. A method for inhibiting SH2 domain binding comprising exposing a material containing an SH2 domain to a compound of claim 38.

91. A method for determining the presence of an SH2 domain in a material comprising:

- (a) exposing a sample of said material to a SH2 binding compound and obtaining a first binding result;
- (b) exposing another sample of said material to a compound of claim 38 and obtaining a second binding result; and
- (c) comparing the first and second binding results to determine whether an SH2 domain is present in the material.

92. A method of preventing or treating a disease, state, or condition in a mammal comprising administering a compound of claim 38.

106. A method of enhancing the therapeutic effect of a treatment rendered to a mammal that has been afflicted with a disease, state, or condition, comprising administering to the mammal a compound of claim 38 in conjunction with the treatment.

112. A method of inhibiting the MAP kinase activity in a mammal comprising administering to the mammal a compound of claim 38.

115. A compound of the formula:



wherein n is 0 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, and a carboxyl end, the phenyl ring having (i) dicarboxy C<sub>1</sub>-C<sub>6</sub> alkyl, (ii) hydroxyl and carboxy C<sub>1</sub>-C<sub>6</sub> alkyl, (iii) carboxyl and carboxy C<sub>1</sub>-C<sub>6</sub> alkyl, or (iv) dicarboxyhalo C<sub>1</sub>-C<sub>6</sub> alkyl, or dicarboxyhalo C<sub>1</sub>-C<sub>6</sub> alkoxy; or an ester of (i), (ii), (iii), or (iv); wherein the alkyl portion of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and keto;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, oxalyl, C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, arylaminooxalyl, aryl C<sub>1</sub>-C<sub>6</sub> alkylaminooxalyl, C<sub>1</sub>-C<sub>6</sub> alkoxyoxalyl, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, heterocyclyl carbonyl, heterocycl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl heterocycl C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl, aryloxy carbonyl, and aryl C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy,

and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

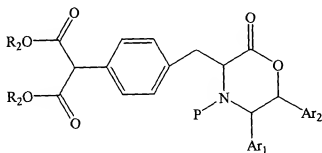
Z is an aryl C<sub>1</sub>-C<sub>6</sub> alkylamino or arylheterocyclyl C<sub>1</sub>-C<sub>6</sub> alkylamino;

or a salt thereof.

116. A composition comprising a pharmacologically acceptable carrier and a compound of claim 115.

117. A method for inhibiting an SH2 domain from binding with a phosphoprotein comprising contacting an SH2 domain with a compound of claim 115.

118. A process for the preparation of a compound of formula VII:



(VII),

wherein R<sub>2</sub> is alkyl, P is an amine protecting group, and Ar<sub>1</sub> and Ar<sub>2</sub> are aryl; the process comprising:

- (a) converting a p-halotoluene to a p-tolyl-malonic acid dialkyl ester by contacting the p-halotoluene with a dialkylmalonate and a cuprous halide;
- (b) halogenating the p-tolyl-malonic acid dialkyl ester to obtain a (4-halomethylphenyl)-malonic acid dialkyl ester; and
- (c) contacting the (4-halomethylphenyl)-malonic acid ester with a benzyl-6-oxo-2,3-diaryl-4-morpholine to obtain the compound of formula VII.